

CLAIMS

1. A human antibody or antibody fragment, which antibody or fragment:
  - (i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of Apolipoprotein E (ApoE-CTD) or the amino acid sequence of a part thereof; and
  - (ii) binds to human plaques.
2. An antibody or antibody fragment according to claim 1, which comprises a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 512, SEQ ID NO: 513, SEQ ID NO: 514, SEQ ID NO: 515, SEQ ID NO: 516 or SEQ ID NO: 517.
3. An antibody or antibody fragment according to claim 1 or 2, which comprises a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 20.
4. An antibody or antibody fragment according to claim 3 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 23 or SEQ ID NO: 26.
5. An antibody or antibody fragment according to claim 1 or 2, wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 373, SEQ ID NO: 374, SEQ ID NO: 375, SEQ ID NO: 376, SEQ ID NO: 485, SEQ ID NO: 486, SEQ ID NO: 487, SEQ ID NO: 488 or SEQ ID NO: 489.
6. An antibody or antibody fragment according to claim 5, wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322 or SEQ ID NO: 373.

7. An antibody or antibody fragment according to claim 1, which comprises a heavy chain CDR3 region comprising an amino acid sequence selected from the sequences shown in SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 50, SEQ ID NO: 53, SEQ ID NO: 56, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 68, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 80, SEQ ID NO: 83, SEQ ID NO: 86 and SEQ ID NO: 89.

8. An antibody or antibody fragment according to claim 7, wherein said CDR3 region comprises SEQ ID NO: 50, SEQ ID NO: 68; SEQ ID NO: 74 or SEQ ID NO: 10 80.

9. An antibody or antibody fragment according to any one of claims 1 to 8, wherein said polypeptide having the amino acid sequence of a part of SEQ ID NO: 1 comprises the sequence shown in SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, or SEQ ID NO: 17.

10. An antibody or antibody fragment according to any one of claims 1 to 8, wherein said polypeptide having the amino acid sequence of a part of SEQ ID NO: 1 comprises the sequence shown in SEQ ID NO: 18 or SEQ ID NO: 19.

11. An antibody or antibody fragment according to any one of claims 1 to 8, which binds to said polypeptide having the amino acid sequence shown in SEQ ID NO: 1.

25 12 A human antibody or antibody fragment, which antibody or fragment:

(i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of ApoE-CTD or the amino acid sequence of a part thereof; and

(ii) comprises a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 512, SEQ ID NO: 513, SEQ ID NO: 514, SEQ ID NO: 515, SEQ ID NO: 516 or SEQ ID NO: 517.

13. An antibody or antibody fragment according to claim 12 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 20.

5 14. An antibody or antibody fragment according to claim 13 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 23 or SEQ ID NO: 26.

10 15. An antibody or antibody fragment according to claim 12 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 373, SEQ ID NO: 374, SEQ ID NO: 375, SEQ ID NO: 376, SEQ ID NO: 485, SEQ ID NO: 486, SEQ ID NO: 487, SEQ ID NO: 488 or SEQ ID NO: 489.

15 16. An antibody or antibody fragment according to claim 15 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322 or SEQ ID NO: 373.

17. A human antibody or antibody fragment, which antibody or fragment:

20 (i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of ApoE-CTD or the amino acid sequence of a part thereof; and  
(ii) comprises a heavy chain CDR3 region comprising an amino acid sequence selected from the sequences shown in SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 50, SEQ ID NO: 53, SEQ ID NO: 56, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 68, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 80, SEQ ID NO: 83, SEQ ID NO: 86 and SEQ ID NO: 89.

25 30 18. An antibody or antibody fragment according to any one of the preceding claims, which binds to said polypeptide in the presence of very low density lipoprotein (VLDL).

19. A human antibody or antibody fragment, which antibody or fragment binds, in the presence of VLDL, to a polypeptide having the ApoE-CTD amino acid sequence shown in SEQ ID NO: 1 or the amino sequence of a part thereof.
- 5 20. An antibody or antibody fragment according to any one of the preceding claims, wherein said polypeptide is a recombinant polypeptide.
- 10 21. An antibody or antibody fragment according to claim 14, wherein said recombinant polypeptide is biotinylated.
- 15 22. A human antibody or antibody fragment, which antibody or fragment:
  - (i) binds to human plaques; and
  - (ii) comprises a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 512, SEQ ID NO: 513, SEQ ID NO: 514, SEQ ID NO: 515, SEQ ID NO: 516 or SEQ ID NO: 517.
- 20 23. An antibody or antibody fragment according to claim 22 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 20.
- 25 24. An antibody or antibody fragment according to claim 23 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 23 or SEQ ID NO: 26.
- 25 25. An antibody or antibody fragment according to claim 22 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 373, SEQ ID NO: 374, SEQ ID NO: 375, SEQ ID NO: 376, SEQ ID NO: 485, SEQ ID NO: 486, SEQ ID NO: 487, SEQ ID NO: 488 or SEQ ID NO: 489.
- 30 26. An antibody or antibody fragment according to claim 25 wherein said CDR3 region comprises the sequence shown in SEQ ID NO: 207, SEQ ID NO: 208, SEQ

ID NO: 209, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322 or SEQ ID NO: 373.

27. A human antibody or antibody fragment, which antibody or fragment:

5 (i) binds to human plaques; and  
(ii) comprises a heavy chain CDR3 region comprising an amino acid sequence selected from the sequences shown in SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 50, SEQ ID NO: 53, SEQ ID NO: 56, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 68, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 80, SEQ ID NO: 83, SEQ ID NO: 86 and SEQ ID NO: 89.

28. An antibody or antibody fragment according to any one of the preceding claims, which binds to said plaques in the presence of VLDL.

15 29. An antibody or antibody fragment according to any one of claims 18, 19 and 28, wherein said VLDL is present in human plasma.

30. An antibody or antibody fragment according to claim 29, which binds to the plaques in the presence of 25% plasma.

20 31. An antibody or antibody fragment according to claim 30, which binds to the plaques in the presence of from 25% to 50% plasma.

25 32. An antibody or antibody fragment according to claim 31, which binds to the plaques in the presence of 50% plasma.

33. An antibody or antibody fragment which comprises the heavy chain sequence shown in SEQ ID NO: 136 and the light chain sequence shown in SEQ ID NOS: 521 and 522.

30 34. An antibody or antibody fragment which comprises the heavy chain sequence shown in SEQ ID NO: 142 and the light chain sequence shown in SEQ ID NO: 523.

35. An antibody or antibody fragment which comprises the heavy chain sequence shown in SEQ ID NO: 40 and the light chain sequence shown in SEQ ID NO: 517 and/or 518.

5 36. An antibody or antibody fragment which comprises the heavy chain sequence shown in SEQ ID NO: 40 and the light chain sequence shown in SEQ ID NO: 519 and/or 520.

10 37. An antibody or antibody fragment which comprises the heavy chain CDR1 sequence shown in SEQ ID NO: 24, the heavy chain CDR2 sequence shown in SEQ ID NO: 25 and the heavy chain CDR3 sequence shown in any one of SEQ ID NOS: 207, 209 and 210.

15 38. An antibody or antibody fragment according to claim 37, which comprises the light chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 33, 34 and 35, SEQ ID NOS: 219, 247 and 269, SEQ ID NOS: 226, 252 and 275 or SEQ ID NOS: 218, 34 and 268.

20 39. An antibody or antibody fragment according to claim 38, wherein the heavy chain comprises the sequence shown in SEQ ID NO: 210 and the light chain comprises the sequences shown in SEQ ID NOS: 33, 34 and 35, the heavy chain comprises the sequence shown in SEQ ID NO: 209 and the light chain comprises the sequences shown in SEQ ID NOS: 219, 247 and 269 or SEQ ID NOS: 218, 34 and 268, or the heavy chain comprises the sequence shown in SEQ ID NO: 207 and the light chain comprises the sequence shown in SEQ ID NOS: 226, 252 and 275.

25 40. An antibody or antibody fragment according to any one of claims 37 to 39, wherein the heavy chain comprises the sequence shown in any one of SEQ ID NO: 317, 318 or 319.

41. An antibody or antibody fragment according to any one of claims 38 to 40, wherein the light chain comprises the sequence shown in SEQ ID NO: 43, 295, 294 or 304.

5 42. An antibody or antibody fragment which comprises the heavy chain CDR1 sequence shown in SEQ ID NO: 48, the heavy chain CDR2 sequence shown in SEQ ID NO: 49 and the heavy chain CDR3 sequence shown in any one of SEQ ID NOS: 320, 322 and 323.

10 43. An antibody or antibody fragment according to claim 42, which comprises the light chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 326, 334 and 341, SEQ ID NOS: 93, 333 and 341 or SEQ ID NOS: 325 and 333.

15 44. An antibody or antibody fragment according to claim 43, wherein the heavy chain comprises the sequence shown in SEQ ID NO: 320 and the light chain comprises the sequences shown in SEQ ID NOS: 93, 333 and 341 or SEQ ID NOS: 325, 333 and 341, the heavy chain comprises the sequence shown in SEQ ID NO: 322 and the light chain comprises the sequences shown in SEQ ID NOS: 326, 334 and 341, SEQ ID NOS: 93, 333 and 341 or SEQ ID NOS: 325, 333 and 341, or the heavy chain comprises the sequence shown in SEQ ID NO: 323 and the light chain comprises the sequence shown in SEQ ID NOS: 93, 333 and 341.

20 45. An antibody or antibody fragment according to any one of claims 42 to 44, wherein the heavy chain sequence comprises the sequence shown in SEQ ID NO: 369, 370, 371 or 372.

25 46. An antibody or antibody fragment according to any one of claims 43 to 45, wherein the light chain comprises the sequence shown in SEQ ID NO: 347, 348, 357 or 362.

47. An antibody or antibody fragment which comprises the heavy chain CDR1 sequence shown in SEQ ID NO: 66, the heavy chain CDR2 sequence shown in SEQ ID NO: 67 and the heavy chain CDR3 sequence shown in SEQ ID NO: 373.

5 48. An antibody or antibody fragment according to claim 47, which comprises the light chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 391, 382 and 378 or SEQ ID NOS: 394, 386 and 378.

10 49. An antibody or antibody fragment according to claim 47 or 48, wherein the heavy chain comprises the sequence shown in SEQ ID NO: 397.

50. An antibody or antibody fragment according to claim 48 or 49 wherein the light chain sequence shown in SEQ ID NO: 406 or 418.

15 51. An antibody or antibody fragment according to any one of the preceding claims, wherein said antibody is an IgG.

52. An antibody or antibody fragment according to any one of claims 1 to 50, wherein said antibody fragment is a Fab fragment or scFv.

20 53. An antibody or antibody fragment according to any one of the preceding claims which is a monoclonal antibody.

54. An antibody or antibody fragment according to any one of the preceding 25 claims which is a humanised antibody.

55. An antibody or antibody fragment according to any one of the preceding claims which is chimeric.

30 56. An antibody or antibody fragment according to any one of the preceding claims, for use in a method of treatment of the human or animal body by therapy or in a diagnostic method practised on the human or animal body.

57. Use of an antibody or antibody fragment according to any one of claims 1 to 55, in the manufacture of a medicament for the treatment or prevention of an amyloid disorder.

5 58. Use according to claim 57, wherein the amyloid disorder is selected from Alzheimer's disease, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, familial amyloid polyneuropathy III, familial non-neuropathic amyloidosis, hereditary cerebral amyloid angiopathy, Familial British Dementia (FBD), Haemodialysis-related 10 amyloidosis, Familial amyloidosis (Finnish type), Familial subepithelial corneal amyloid, Type II diabetes, Hereditary renal amyloidosis, Pituitary-gland amyloidosis, injection localized amyloidosis, Medullary carcinoma of the thyroid, Atrial amyloidosis, Familial Danish Dementia (FDD), Downs syndrome, Spongiform 15 encephalopathies, Sporadic Creutzfeldt-Jakob disease, Familial Creutzfeldt-Jakob disease, Iatropic prion disorders, Variant Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker Disease (GSS), Kuru, Parkinson's disease, Huntington's disease, Familial amyotrophic lateral sclerosis (ALS) and Chronic obstructive pulmonary disease.

20 59. A pharmaceutical composition comprising an antibody or antibody fragment according to any one of claims 1 to 55 and a pharmaceutically acceptable carrier or diluent.

25 60. A method of treating a subject suffering from an amyloid disorder comprising administering to said subject a therapeutically effective amount of an antibody or antibody fragment according to any one of claims 1 to 55.

30 61. A method of diagnosing an amyloid disorder in a subject comprising:  
(i) administering to said subject an antibody or antibody fragment according to any one of claims 1 to 55; and  
(ii) determining whether or not said antibody or antibody fragment binds

to plaques in said subject, wherein binding of said antibody or antibody fragment to plaques is indicative of an amyloid disorder, thereby determining whether the subject has an amyloid disorder.

5 62. A method according to claim 61 wherein said antibody or antibody fragment is labelled.

63. A method according to claim 60 or 61 wherein the amyloid disorder is selected from Alzheimer's disease, primary systemic amyloidosis, secondary 10 systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, familial amyloid polyneuropathy III, familial non-neuropathic amyloidosis, hereditary cerebral amyloid angiopathy, Familial British Dementia (FBD), Haemodialysis-related amyloidosis, Familial amyloidosis (Finnish type), Familial subepithelial corneal amyloid, Type II diabetes, Hereditary renal amyloidosis, 15 Pituitary-gland amyloidosis, injection localized amyloidosis, Medullary carcinoma of the thyroid, Atrial amyloidosis, Familial Danish Dementia (FDD), Downs syndrome, Spongiform encephalopathies, Sporadic Creutzfeldt-Jakob disease, Familial Creutzfeldt-Jakob disease, Iatropic prion disorders, Variant Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker Disease (GSS), Kuru, Parkinson's 20 disease, Huntington's disease, Familial amyotrophic lateral sclerosis (ALS) and Chronic obstructive pulmonary disease.

64. A polynucleotide encoding an antibody or antibody fragment according to any one of claims 1 to 55.

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65. A vector comprising a polynucleotide according to claim 64.

66. A host cell expressing a polypeptide according to any one of claims 1 to 55.

30 67. A virus encoding a polynucleotide according to claim 64.

68. A kit for detecting ApoE-CTD, which kit comprises an antibody or antibody fragment according to any one of claims 1 to 55 and means for detecting said an antibody or antibody fragment.

5 69. A method for detecting the presence of ApoE-CTD in a sample from a subject, which method comprises:

(i) contacting a sample taken from a subject with an antibody or antibody fragment according to any one of claims 1 to 55 under conditions that permit binding of the an antibody or antibody fragment to ApoE-CTD; and

10 (ii) determining whether or not the an antibody or antibody fragment binds to the sample thereby detecting any ApoE-CTD present in the sample.